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Datasheet for the decision of 27 October 2016

Case Number: T 1954/12 - 3.3.08

Application Number: 07109353.8

Publication Number: 1842920

IPC: C12N15/68, C12N9/04

Language of the proceedings: EN

Title of invention:
Cells coexpressing vitamin K reductase and vitamin K dependent protein and use thereof to improve the productivity of said vitamin K dependent protein

Patent Proprietor:
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Opponent:
Baxter Innovations GmbH

Headword:
Recombinant vitamin K epoxide reductase/UNIVERSITY NORTH CAROLINA

Relevant legal provisions:
EPC Art. 123(2), 76(1), 123(3), 64(2), 84, 83, 87, 54, 56
EPC R. 80

Keyword:
Main Request - meets all requirements of the EPC (yes)

Decisions cited:
G 0002/88, G 0002/98, G 0003/14, T 0401/95, T 0190/99, T 0282/09

Catchword:

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Case Number: T 1954/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 27 October 2016

Appellant I: (Patent Proprietor)	UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL 308 Bynum Hall, Campus Box 4105 Chapel Hill, NC 27599-4105 (US)
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Appellant II: (Opponent)	Baxter Innovations GmbH Industriestrasse 67 1221 Wien (AT)
Representative:	Engelhard, E. Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 July 2012 concerning maintenance of the European Patent No. 1842920 in amended form.**

Composition of the Board:

Chairman M. Wieser
Members: P. Julià
J. Geschwind

Summary of Facts and Submissions

I. European patent no. 1 842 920 is based on European patent application no. 07 109 353.8 (hereinafter "*the application as filed*"), a divisional application of European patent application 04 789 039.7 (originally published as International patent application WO 2005/030039, hereinafter "*the parent application*"). The patent was granted with seven claims and claimed the priority of document US 505 527 P, having the filing date of 23 September 2003.

II. An opposition was filed on the grounds of Articles 100(a), (b) and (c) EPC. The opposition division decided that the main request contravened Article 54 EPC. The patent was maintained on the basis of an auxiliary request 1 filed at the oral proceedings on 24 May 2012.

III. Appeals were lodged by the patent proprietor and the opponent (appellants I and II, respectively). In the statement setting out the grounds of appeal, appellant I filed a main request and auxiliary requests A and B. Auxiliary request B was identical to the request upheld by the opposition division.

IV. Each of the appellants filed a reply to the other party's statement of grounds of appeal. In its reply, appellant I filed further documentary evidence and auxiliary request C.

V. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), they were informed of the preliminary, non-binding opinion of the board on some of the issues of the case.

VI. In reply thereto, appellant I filed further substantive submissions, a new main request and auxiliary requests A, B and C. The main request was identical to the request upheld by the opposition division.

VII. Oral proceedings were held on 27 October 2016. At the beginning of these proceedings, appellant I withdrew auxiliary request B.

VIII. Claims 3 to 7 **as granted** read as follows:

"3. A cell that contains and expresses a recombinant nucleic acid comprising a nucleic acid encoding vitamin K epoxide reductase operatively associated with a heterologous promoter."

4. A method for improving the productivity of vitamin K dependent protein expression in a host cell, comprising the steps of:

(a) introducing into a host cell a nucleic acid encoding a vitamin K dependent protein;
(b) introducing into the host cell a recombinant nucleic acid encoding a vitamin K epoxide reductase (VKOR) and a recombinant nucleic acid encoding a vitamin K dependent carboxylase; and
(c) expressing the nucleic acids of steps (a) and (b).

5. A method for improving the productivity of vitamin K dependent protein expression in a host cell, comprising the steps of:

(a) providing a host cell that expresses a nucleic acid encoding a vitamin K dependent protein;

(b) introducing a recombinant nucleic acid coding for a vitamin K epoxide reductase (VKOR) into the host cell and a recombinant nucleic acid encoding a vitamin K dependent carboxylase; and
(c) expressing the nucleic acids of steps (a) and (b).

6. A method for improving the productivity of vitamin K dependent protein expression in a host cell, comprising the steps of:

(a) providing a host cell that expresses a heterologous nucleic acid encoding a vitamin K epoxide reductase (VKOR);
(b) introducing a nucleic acid coding for a vitamin K dependent protein into the host cell and a nucleic acid encoding a vitamin K dependent carboxylase; and
(c) expressing the nucleic acids of steps (a) and (b).

7. A method according to any one of claims 4, 5 or 6 wherein the nucleic acid encoding the Vitamin K dependent protein is selected from the group comprising factor VII, factor IX, factor X, prothrombin, Protein C and Protein S."

IX. The **main request** consists of three claims which read as follows:

"1. A cell that contains and expresses a recombinant nucleic acid comprising a nucleic acid encoding vitamin K epoxide reductase operatively associated with a heterologous promoter, and further contains and expresses a heterologous nucleic acid encoding vitamin K dependent carboxylase and expresses a nucleic acid encoding a vitamin K dependent protein, wherein said vitamin K epoxide reductase converts vitamin K epoxide to vitamin K.

2. A method of making a vitamin K dependent protein which comprises culturing a host cell that expresses a nucleic acid encoding a vitamin K dependent protein in the presence of vitamin K and produces a vitamin K dependent protein, and then harvesting the vitamin K dependent protein from the culture, the host cell containing and expressing a heterologous nucleic acid encoding vitamin K dependent carboxylase, and the host cell further containing and expressing a heterologous nucleic acid encoding vitamin K epoxide reductase (VKOR).

3. A method according to claim 2 wherein the nucleic acid encoding the Vitamin K dependent protein is selected from the group comprising factor VII, factor IX, factor X, prothrombin, Protein C and Protein S."

X. The following documents are cited in this decision:

D4: WO 00/03015 (publication date: 20 January 2000);

D5: N. Wajih *et al.*, J. Biol. Chem., 11 June 2004, Vol. 279, No. 24, pages 25276 to 25283;

D6: WO 92/01795 (publication date: 6 February 1992);

D7: A. Fregin *et al.*, Blood, 2002, Vol. 100, pages 3229 to 3232;

D29: Y-M. Sun *et al.*, Blood, 2005, Vol. 106, pages 3811 to 3815.

XI. The submissions of appellant I, insofar as they are relevant to the present decision, may be summarized as follows:

Main request
Rule 80 EPC; Claim 1

The functional feature "*wherein said vitamin K epoxide reductase converts vitamin K epoxide to vitamin K*" has been introduced into claim 1 to address objections raised under Articles 54 and 83 EPC.

Articles 123(2) and 76(1) EPC; Claim 1

The nucleic acid sequence encoding the vitamin K epoxide reductase (VKOR) was disclosed in Example 10 of the application as filed and of the parent application. The name "*VKOR protein*" was derived from the ability of this protein to reduce vitamin K epoxide to vitamin K. The disclosure of the application as filed and of the parent application as a whole, was concerned with the feature that has been introduced into claim 1. As shown in Example 10, the introduction and expression of the identified nucleic acid sequence into a cell, which did not have the ability to reduce vitamin K epoxide to vitamin K, provided this cell with said ability. The claimed subject-matter was not a new, undisclosed intermediate generalization.

Article 123(3) EPC; Claims 2 and 3

Granted claim 3 was a product-claim directed to a cell containing and expressing a nucleic acid encoding VKOR. According to decision G 2/88 (EPO OJ 1990, page 93), the protection conferred by a product-claim was absolute and, depending on the facts and technical features of the claim, this protection extended to methods using this product as starting material. A change of category of a product-claim to a method-claim

did not contravene the EPC and was allowable (*inter alia*, T 401/95 of 28 January 1999, and T 282/09 of 31 March 2011). Although granted claims 4-7 were directed to a method for improving the productivity of vitamin K dependent (VKD) protein expression, the result of these methods, the final product, was always a VKD protein. According to Article 64(2) EPC, the protection conferred by granted claims 4-7 extended also to the product obtained by these methods, i.e. a VKD protein. The change of category of granted claim 3 to a method using the cell of this claim for the production of a VKD protein, such as the method of claim 2 of the main request, did not thus extend the protection conferred because the resulting product of this method (VKD protein) was identical to the product obtained by the methods of granted claims 4-7. Moreover, claim 2 included features (harvesting) which further limited the scope of protection *vis-à-vis* granted claims 4-7.

There was no evidence on file showing that the sequence or order of the steps carried out in the methods of granted claims 4-7 resulted in different products. The references to a reduced carboxylation rate and to the presence of under-carboxylated VKD proteins made in the patent and in document D5 were of no relevance for the claimed methods as they related to methods wherein an inhibitor (warfarin) was present. The disclosure of document D29 showed that the sequence or order of the method steps had a quantitative effect (efficiency of transformation) but not a qualitative influence, in the sense that different products were obtained.

Moreover, claim 2 and granted claims 4-7 (even though citing several method steps) did not specify the sequence or order in which the method steps were carried out, which was also in line with the disclosure

of the patent (paragraph [0041], lines 36 to 39). In the light of this disclosure and construing the claims by a mind willing to understand (T 190/99 of 6 March 2001), the improvement referred to in granted claims 4-7 was achieved by introducing and expressing a nucleic acid encoding VKOR into a cell. The improvement was always in relation to a cell that did not contain such a nucleic acid and was thus an automatic consequence of the presence of a nucleic acid encoding VKOR. Therefore, claim 2, by requiring the presence of such a nucleic acid in the cell, was also directed to a method for improving the productivity of a VKD protein.

Articles 84 EPC; Claim 1

VKOR activity assays had long been known in the art and Example 3 of the patent (entitled "*VKOR activity assay*") disclosed how the conversion of vitamin K epoxide to vitamin K was assayed. The abbreviation VKOR was present in the granted claims and not open to an objection under Article 84 EPC.

Article 83 EPC; Claims 1-3

There was no evidence on file showing that a skilled person could not put the invention into practice.

Article 87 EPC; Claims 2 and 3

Whilst the priority document disclosed a method of making VKD protein which comprised culturing a cell expressing a VKD protein in presence of vitamin K (page 2, line 30 to page 3, line 3), claim 2 required the claimed cell to express a nucleic acid encoding a VKD protein. Neither the priority document nor claim 2 used in this context the term "*heterologous*". A skilled

person reading the priority document knew from its common general knowledge that, for a protein to be expressed and harvested, it had to be produced from a nucleic acid encoding it (i.e. the subject-matter of claim 2). Thus, in the light of the disclosure of the priority document taken as a whole and of the common general knowledge, the subject-matter of claims 2 and 3 was directly and unambiguously disclosed in the priority document and entitled to the claimed priority date. Both, the priority document and the claims, related to the same invention (G 2/98, OJ EPO 2001, page 413).

Article 56 EPC; Claims 1-3

The closest state of the art, document D6, disclosed methods to obtain VKD carboxylase, but not the complete nucleotide sequence of the gene encoding it. It was stated that, once this nucleotide sequence was obtained, it could be expressed in cells, along with VKD protein sequences known in the art, to produce VKD proteins. Document D6 did not teach how to obtain VKOR and did not provide any VKOR or VKOR activity. The problem to be solved by the present invention was to provide and alternative method for the production of VKD proteins. According to the case law, it was not necessary to show any advantage or surprising effect for an alternative method to be based on an inventive concept. However, in the present case, there was post-published evidence on file (such as document D29) demonstrating the advantages of the claimed method over other methods known in the art. Evidence was also on file showing that a skilled person could not have a reasonable expectation of success when attempting to isolate a nucleic acid encoding VKOR. As stated in document D6, VKOR activity was already known in the

art, but based on the difficulty to purify VKOR, it was widely believed that a multicomponent enzyme complex was responsible for this activity rather than a single enzyme. In document D7, several genes were considered to be involved in familial multiple coagulation factor deficiency (FMFD) and emphasis was put on the role of a glutathione-S-transferase (GST) gene that had been suggested to be a member of the multiprotein complex associated with the VKOR activity. However, the VKOR gene identified in the patent, which encoded a single enzyme associated with the VKOR activity, was not this GST gene.

XII. The submissions of appellant II, insofar as they are relevant to the present decision, may be summarized as follows:

Main request
Rule 80 EPC; Claim 1

If the feature "*wherein said vitamin K epoxide reductase converts vitamin K epoxide to vitamin K*" introduced in claim 1 was implicit to all VKORs and thus already encompassed by the scope of granted claim 3, this feature was not suitable to address any ground of opposition. However, if this feature constituted a limitation to the granted claim, it had to fulfil the formal requirements of the EPC, which it did not.

Articles 123(2) and 76(1) EPC; Claim 1

The feature "*wherein said vitamin K epoxide reductase converts vitamin K epoxide to vitamin K*" had no basis in the application as filed or in the parent application. It had been taken from the background sections of these documents and was cited and stood in

no apparent context with the language of the claims. There was no reference to the "*VKOR of the invention*" in this section, which referred to "*human diet*" and was thus limited to endogenous human VKOR (page 2, paragraph [0004] of the application as filed; page 2, lines 3 to 5 of the parent application). This was not a basis for a recombinant VKOR expression from any species, in any host cell and with any heterologous promoter. Figure 3 and the corresponding text in Example 9 also did not provide this basis because they were limited to a specific form of VKOR nucleic acid (mGC11276 cDNA) transfected in specific Sf9 cells. None of these limitations was present in claim 1. Example 9 could not be used for a generalization because the conditions required by the case law were not fulfilled. The references to several isoforms encoded by the VKOR gene and the need to characterize the activity and expression pattern of each isoform were highly relevant features since they demonstrated that the specific situations disclosed in the examples could not be transferred to other situations.

Article 123(3) EPC; Claims 2 and 3

Granted claims 4-7 were directed to methods for improving the productivity of VKD protein expression and not to the production of a VKD protein. This feature could not be disregarded because it excluded from the scope of protection all methods that did not provide an improvement. Granted claims 4-7 were characterized by several steps that had to be carried out in a particular order or sequence that was essential for obtaining this improvement. Granted claim 3 was directed to a cell containing and expressing a recombinant VKOR nucleic acid without referring to these sequential steps.

Claim 2 of the main request was a method-claim that did not contain any of the sequential steps required in granted claims 4-7. Thus, the method of claim 2 could be carried out by simultaneous introduction of nucleic acids encoding the VKOR, the VKD carboxylase and the VKD protein. This embodiment was not covered by the granted claims. Claim 2 did not require any improvement in the expression of VKD proteins but only the production of these proteins. The scope of this claim was thus broader when compared to the granted claims, because it included methods in which the VKD protein was made but in which no improvement was achieved. The mere introduction of a nucleic acid encoding VKOR did not directly provide an improvement because the method had to be carried out under optimal conditions (pH, temperature, etc.) and with appropriate elements and compositions (media, supplements, etc.).

While granted claims 4-7 were directed to methods for achieving an effect (improving productivity of a VKD protein), claim 2 was directed to the mere production of a VKD protein. According to Article 64(2) EPC, the scope of protection of claim 2 extended to the product obtained by the method. However, this was not the case for granted claims 4-7 and thus, an extension of the protection conferred was given. Moreover, the sequence of the method steps indicated in granted claims 4-7 was essential not only for achieving an improved activity and expression of the product but also for its properties. The levels of carboxylation of the VKD protein depended on the order in which these steps were carried out. As stated in the patent (paragraph [0002], last sentence) and shown also in documents D29 and D5 (page 3812, left-hand column, last paragraph, and page 25277, left-hand column, lines 44 to 48, respectively),

even if the starting material in all methods was a cell, different products were achieved depending on the actual set of conditions used and on the order or sequence of the method steps used to obtain this cell.

Claim 3 as granted was a product-claim directed to a cell. This product-claim did not encompass any and all possible methods and uses in which this product could be used. The possibility to change claim category from a product-claim to a method or use-claim did not allow to arbitrarily change to any possible method and use at will. According to decision G 2/88 (*supra*), a use-claim was only covered by the scope of the granted product-claim, if it was a use to achieve an effect but not to produce a product. If the use-claim related to a use to produce a product, then the use led to a different physical entity (a different product) that was not covered by the granted claims. The methods of claims 2 and 3 of the main request were directed to a "*method of making*" and not to a use for achieving an effect. They were directed to make a VKD protein, a different physical entity than the cell of granted claim 3. Therefore, claims 2 and 3 of the main request extended the protection conferred by the granted claims.

Article 84 EPC; Claim 1

The patent did not disclose how to measure the conversion required by the feature "*wherein said vitamin K epoxide reductase converts vitamin K epoxide to vitamin K*". There was a sole vague statement to such measurement in the patent and no specific method or assay was described therein (paragraph [00034]). Moreover, the nucleic acid encoding VKOR was not defined by any specific nucleotide sequence in claim 1.

Article 83 EPC; Claims 1 to 3

The patent did not provide enough information to enable a skilled person to carry out the alleged invention. Key features were missing for providing guidance how to carry out the invention over the whole breadth of the claims.

Article 87 EPC; Claims 2 and 3

According to claim 2, the host cell expressed "*a nucleic acid encoding a vitamin K dependent protein*". Claim 11 of the priority document simply required the expression of a VKD protein and encompassed thereby a situation where the host cell had, and expressed, an endogenous VKD protein (cf. paragraph bridging pages 2-3, claim 11 of the priority document). Contrary thereto, claim 2 comprised the expression of both, an endogenous and a heterogenous nucleic acid.

Article 56 EPC; Claims 1 to 3

The closest state of the art, document D6, disclosed a method to increase the production of VKD proteins in cultured cells by expressing a nucleic acid sequence encoding a gamma-carboxylase (page 3, lines 29 to 32; page 4, lines 22 to 33). The activity of a reductase which regenerated vitamin K hydroquinone, required for the carboxylation of glutamic residues, was also mentioned (page 2, lines 2 and 3). Starting therefrom, the technical problem to be solved was the provision of further means and methods for producing VKD proteins. The solution according to claims 1-3 was in no way advantageous over the disclosure of document D6. The single feature differentiating the claimed subject-matter from this prior art was the provision of the

sequence of the VKOR gene. However, document D6 already comprised a pointer to the existence of this reductase and it was thus obvious for a skilled person to go for its sequence by applying well-known cloning methods. In the absence of any advantages associated with the provision of the sequence of the VKOR gene, no inventive step could be acknowledged to the subject-matter of the claims.

XIII. The patent proprietor requested that the appeal of the opponent be dismissed.

XIV. The opponent requested that the decision under appeal be set aside and the patent revoked.

Reasons for the Decision

Main Request
Rule 80 EPC; Claim 1

1. The functional feature "*wherein said vitamin K epoxide reductase converts vitamin K epoxide to vitamin K*" present in claim 1 addresses objections raised under several articles of the EPC, in particular lack of novelty over document D4 (Article 54(3) EPC) and insufficiency of disclosure (Article 83 EPC). The introduction of this feature into claim 1 was thus occasioned by grounds of appeal and the requirements of Rule 80 EPC are fulfilled.

Articles 123(2) and 76(1) EPC; Claims 1-3

2. The VKOR function or activity is first mentioned in the application as filed in the section referring to the background of the invention (cf. page 2, lines 30-32).

The importance of having an "*active form of the protein*", "*a biologically active fragment or polypeptide*", "*a functional homologue*", etc. is emphasized throughout the entire description (cf. *inter alia*, page 5, lines 52-54, page 6, lines 24-26, page 7, lines 22-23), which explicitly states that "[t]*he biological activity ... can be determined according to the methods provided herein and as are known in the art for identifying VKOR activity*" (cf. page 6, lines 29-31). A standard "*VKOR activity assay*", described in Example 4 of the application, is based on the conversion of vitamin K epoxide [KO] to vitamin K (cf. page 11, paragraph [0083]), i.e. the functional feature present in claim 1. This activity is also the VKOR activity measured for screening several cell lines (Example 8), for detecting siRNA inhibition in A549 cells (Example 9; Figures 2-3), and for identifying the "*recombinant nucleic acid encoding VKOR*" in Sf9 cells (Example 10; Figures 4-5). There is no other VKOR function or activity disclosed in the application as filed and the reference to "*characterize the activity*" of "*several [VKOR] isoforms*" must be understood in this context (cf. page 13, paragraph [0094]). The more so since enzymatic isoforms usually perform the same biochemical function, although often at different rates. The disclosure of the application as filed is also found in the parent application, *inter alia*, on page 9, lines 29-31, page 11, lines 3 and 8-11, page 13, lines 13-14, page 23 for Example 4, page 24 for Example 8, page 25 for Example 9 and page 26 for Example 10.

3. For the subject-matter of the method claims 2 and 3, basis is found on page 3, lines 47-52 and page 7, lines 28-50 of the application as filed, and on page 5, lines 1-8, page 13, line 22 to page 14, line 16, and claims

12 and 13 of the parent application. None of the features and/or limitations referred to by appellant II (host cell, heterologous promoter, etc.; cf. point XII *supra*) is present in the general disclosure of the application as filed or the parent application and, in particular, not in the claims of the application as filed (claims 1-8) and of the parent application (claims 12 and 13).

4. Thus, the requirements of Articles 123(2) and 76(1) EPC are fulfilled.

Article 123(3) EPC; Claims 2 and 3

5. According to decision G 2/88 (OJ EPO 1990, page 93), "*a patent which claims a physical entity per se, confers absolute protection upon such physical entity; that is, wherever it exists and whatever its context (and therefore for all uses of such physical entity, whether known or unknown)*". In accordance therewith, it follows that "*a claim to a particular use of a compound is in effect a claim to the physical entity (the compound) only when it is being used in the course of the particular physical activity (the use), this being an additional technical feature of the claim. Such a claim therefore confers less protection than a claim to the physical entity per se*". Thus, "*a change of category from a claim to a physical entity per se ... to a physical activity involving the use of such physical entity, therefore does not extend the protection conferred by the patent, and is admissible*" (cf. point 5 of the Reasons). However, a distinction is made between "*a patent whose claimed subject-matter is the use of a product to achieve an effect ...* [and] *... a patent whose claimed technical subject-matter is a process of manufacture of a product*". For this latter

case, it is stated with reference to Article 64(2) EPC that "*protection is conferred not only upon the claimed process of manufacture, but also upon the product resulting directly from the manufacture*" (cf. point 5.1 of the Reasons).

6. Indeed, it is also established in this decision that, when assessing Article 123(3) EPC, "*it is the totality of the claims before amendment in comparison with the totality of the claims after the proposed amendment that has to be considered*" (cf. point 3.2 of the Reasons). In this context, it is further stated that an amendment may involve *"a change of category, or a change in the technical features of the invention, or both*". In the latter case, it has to be assessed whether the features concerned are more or less narrowly defined as a result of the amendment (cf. point 4.1 of the Reasons).

7. Granted claim 3 is a product-claim in which the physical entity is a cell that contains and expresses a recombinant nucleic acid encoding a VKOR (cf. point VIII *supra*). There is no reference in granted claim 3 to the presence of other recombinant nucleic acids, such as those encoding a VKD carboxylase and/or a VKD protein. That means that, although their presence is not excluded, the claim is not limited to a cell obligatory containing them. Contrary thereto, the cell of claim 1 of the main request is further limited by the presence of these two specific nucleic acids and, in this respect, is more narrowly defined and does not extend the protection conferred. This has not been contested in the appeal procedure.

8. Likewise, there is no reference in granted claim 3 to any method of production of the claimed cell and thus,

it may be produced by any possible method, including all methods disclosed in the patent. This includes, in particular, a method in which a recombinant nucleic acid encoding VKOR is introduced into a cell simultaneously with two other nucleic acids (encoding a VKD protein and a VKD decarboxylase), and methods in which the recombinant nucleic acid encoding the VKOR is introduced into a cell by following several defined sequential steps. All these methods result in a cell falling within the scope of granted claim 3, characterized solely by the presence of a recombinant nucleic acid encoding VKOR.

9. According to decision G 2/88 (*supra*), granted claim 3 confers absolute protection upon the claimed cell and a change of category of this claim to a claim directed to the use of this cell is, in principle, admissible and does not extend the protection conferred. Indeed, such a use is the subject-matter of claims 2 and 3, in which the cell of granted claim 3 (with a recombinant nucleic acid encoding VKOR and with two additional recombinant nucleic acids) is used for making a VKD protein. As in granted claim 3, there is no indication in the methods of claims 2 and 3 as regards the method of production of the cell (i.e. whether the recombinant nucleic acid encoding VKOR is introduced simultaneously with the other two recombinant nucleic acids or following several sequential steps). In fact, there is no need for such indication as these claims are directed to the use of the cell of granted claim 3 and not to a method for its production.

10. Following the distinction made for use-claims in decision G 2/88 (*supra*), the methods of claims 2 and 3 are directed to the manufacture of a particular product, namely a VKD protein, and thus, the protection

conferred by these claims is not limited to the claimed process of manufacture but extends also to this product. The protection conferred by granted claim 3 does not extend to this product and, in this regard, the protection conferred by claims 2 and 3 goes beyond the protection conferred by granted claim 3. However, decision G 2/88 (*supra*) requires to compare the totality of the claims before and after the amendment (cf. point 6 *supra*). In doing so, the methods referred to in granted claims 4-7 are highly relevant and, the board comes to the conclusion, that they provide protection for the product obtained by the methods of claims 2 and 3 of the main request, namely a VKD protein.

10.1 Although the methods of granted claims 4-7 are, in principle, directed to the achievement of a specific effect, namely the improvement in the productivity of VKD protein expression in a host cell, this cannot change the fact that the actual final product obtained by these methods is a VKD protein. Therefore, these claims must be considered as being directed to methods for the production, indeed, an improved productivity, of a VKD protein. Thereby, the protection conferred by these claims extends, in accordance to Article 64(2) EPC, to the product obtained, i.e. a VKD protein.

10.2 Granted claims 4-7 do not only define the use of a specific cell for a certain purpose, they also contain features related to the production of said cell. In particular, they explicitly refer to several steps concerning the introduction of the three nucleic acids required in the methods of these claims, namely the nucleic acids encoding VKOR, VKD carboxylase and VKD protein. Appellant II argues that depending on the manner in which these steps are carried out, either

sequentially or simultaneously, the resulting final product has different properties. In particular, appellant II refers to a different degree or level of carboxylation of the obtained VKD protein. According to appellant II, claims 2 and 3 comprise an embodiment in which all three nucleic acids are introduced simultaneously, which is not covered by granted claims 4-7. This is however contested by appellant I. In any case, following appellant II's argument, the product resulting from this embodiment is different from the product obtained from any of the methods of granted claims 4-7 (wherein several method steps are carried out in a specific sequence or order) and is not covered by the granted claims.

10.3 The board notes, that there is no evidence on file demonstrating that the VKD protein obtained by the "simultaneous" embodiment referred to by appellant II, is structurally different from a VKD protein obtained by the sequential introduction of the three nucleic acids, in whatever chronological order.

10.3.1 Post-published document D29, cited as expert opinion, refers to the transfection of a HEK293 cell line expressing a human Factor X (FX) with recombinant nucleic acids encoding VKOR and a gamma-glutamyl carboxylase (GGCX), either simultaneously or in sequential order. Whereas differences are found in the efficiency of transfection and the number of transfected (resistant) colonies obtained (cf. page 3812, left-hand column, last paragraph), there is no reference to a possible distinction in the level of FX carboxylation obtained, which is disclosed to be "*essentially fully carboxylated*" (cf. page 3813, left-hand column, first paragraph).

10.3.2 Whilst differences in the levels of carboxylation of VKD proteins are reported in the post-published document D5 (cited as expert opinion), the experiments reported in this document are concerned with the effect of a known inhibitor (calumenin) on the VKOR and VKD carboxylase system. Indeed, these results are also described in paragraph [0002] of the patent, wherein, with reference to methods carried out in presence of an inhibitor (warfarin), a reduced rate of carboxylation is reported. However, this has no bearing whatsoever on the methods disclosed in the patent because results of methods carried out in the presence of an inhibitor cannot be directly extrapolated to methods performed in absence of this inhibitor.

10.3.3 The board agrees with appellant II that the actual conditions and components used in performing these methods may influence the degree of carboxylation of the VKD protein obtained. However, the board also observes that neither granted claims 4-7 nor claims 2 and 3 of the main request are limited to any of these conditions and components. Therefore, also in this respect, the scope of protection conferred by claims 2-3 of the main request is not extended when compared with the protection conferred by the granted method claims 4-7.

11. Thus, it follows that the requirements of Article 123(3) EPC are fulfilled.

Article 84 EPC; Claim 1

12. The objection raised by appellant II under Article 84 EPC concerns the functional feature in claim 1, defining VKOR activity (see also point 1 *supra*) and is based on the alleged non-availability of an assay to

measure the conversion of vitamin K epoxide to vitamin K when being present in combination with a VKOR nucleic acid which is not defined by a specific nucleotide sequence (cf. point XII *supra*).

13. There is prior art on file disclosing assays for measuring VKOR activity, as acknowledged also in paragraph [0034], lines 50 and 51 of the patent. Indeed, the patent itself discloses a VKOR activity assay in Example 3. Moreover, the abbreviation "*VKOR*", in general and in the context of the function or activity mentioned in claim 1, is already present in the claims as granted and therefore not open to an objection under Article 84 EPC (cf. G 3/14, OJ EPO 2015, page 102).

14. The requirements of Article 84 EPC are thus fulfilled.

Article 83 EPC; Claims 1 to 3

15. Appellant II's submissions with regard to Article 83 EPC are only of a general nature and do not deal in detail with the reasons given by the opposition division for acknowledging sufficiency of disclosure. In particular the references to post-published documents, such as document D29, which clearly support the disclosure of the patent and the assumptions made therein (cf. pages 17-18, points 25-29 of the decision under appeal) are not considered. Under these circumstances, the board has no reason to deviate from the decision of the opposition division as regards this issue and decides that the main request fulfils the requirements of Article 83 EPC.

Article 87 EPC; Claims 2 and 3

16. Appellant II's arguments concerning claims 2 and 3 are based on the absence of the term "*a nucleic acid encoding a vitamin K dependent protein*" in paragraph bridging pages 2-3 and in claim 11 of the priority document. Whilst, according to appellant II, this term now present in claim 2 covers both, an endogenous and a heterogenous nucleic acid, the latter is not disclosed in the priority document (cf. point XII *supra*).

17. The term "*heterologous*" is not used to characterize the nucleic acid encoding the VKD protein, neither in claim 2 nor in the relevant passages of the priority document. Appellant II's interpretation of claim 2 applies in the same way to the corresponding disclosure in the priority document. Even if the term "*a nucleic acid encoding*" is missing in the relevant passages of this document, the expressed VKD protein may be encoded by both, an endogenous or an heterologous nucleic acid. The priority document is completely silent on the source of the expressed VKD protein. Thus, the board sees no reason to deviate from the findings of the opposition division as regards this issue (cf. page 18, point 30 of the decision under appeal) and decides that the subject-matter of claims 1 to 3 is entitled to the claimed priority date.

Article 54 EPC; Claims 1-3

18. Appellant II does not dispute that document D4, a document cited under Article 54(3) EPC against the subject-matter of former claim requests, does not disclose a cell containing the combination of nucleic acids required in the claims of the main request. Thus, the requirements of Article 54 EPC are fulfilled.

Article 56 EPC; Claims 1 to 3

19. Document D6, representing the closest state of the art, is concerned with the partial purification and activity measurement of a gamma-carboxylase from several species (rat, bovine, human) as well as with the determination of the corresponding (partial) nucleic acid and amino acid sequences. The document further refers to a method of producing or increasing the production of a VKD protein comprising culturing of a transfected or transformed cell to express a nucleic acid encoding the gamma-carboxylase and a nucleic acid encoding said VKD protein (cf. *inter alia*, page 3, lines 29-32, page 4, line 22 to page 5, line 2 and claim 17).

20. Starting from the disclosure in this document, the objective technical problem to be solved is the provision of an alternative method for producing VKD proteins. The board is satisfied that the claimed subject-matter provides a solution to this problem.

21. In document D6, explicit reference is made to the relevance of VKOR in the carboxylation of VKD proteins (cf. page 1, line 31 to page 2, line 3, particularly, page 2, lines 2 and 3). It was thus obvious for a skilled person to try to apply what document D6 teaches with regard to gamma-carboxylase to VKOR in order to obtain an alternative method for producing VKD proteins. However, although VKOR activity was widely described and well-known in the prior art, neither has VKOR protein been purified to homogeneity nor has the VKOR gene been identified (one attempt to do so has failed, cf. document D7).

22. Document D7 refers to "*a candidate region*" suspected to be responsible for the familial multiple coagulation factor deficiency (FMFD) and to contain the VKOR gene. However, this region is considered to contain "*approximately 300 annotated genes*" and to be mapped at "*the pericentromeric region of chromosome 16*" (cf. paragraph bridging left and right-hand columns on page 3231 of document D7). Importantly, document D7 permanently describes the VKOR enzyme as being part of a multiprotein or multienzyme complex and an unknown glutathione-S-transferase (GST) enzyme is considered to be a highly relevant subunit of this complex (cf. abstract, paragraph bridging left and right-hand columns on page 3229, page 3231, right-hand column and page 3232 of document D7). In the light of the disclosure in the prior art on file and in view of the assumptions made therein, the board does not see that the skilled person had a reasonable expectation to arrive at the claimed invention when starting from the closest prior art, document D6. There is, therefore, no reason to deviate from the decision of the opposition division as regards this issue (cf. pages 19 and 20, point 37 of the decision under appeal).

23. The main request fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal of the opponent is dismissed.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated